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Clinical issues in paediatric asthma

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One of the main concerns about the use of inhaled corticosteroids to control airway inflammation in paediatric asthma is the potential to inhibit skeletal growth or lung growth of the individual.

Lung Function Growth

Martinez *et al.* (1) followed a cohort of young children and measured lung function at <1 year and at 6 years of age. At each of these time-points, children were also assessed as having either no wheeze (no history of wheezing), or being early wheezers (wheezed in early life, but not at the age of 6 years), late wheezers (no wheezing in early life, but wheezing at the age of 6 years), or persistent wheezers (wheezing from first year of life and still at age 6). In all groups, there was growth in lung function with time. Children with asthma or persistent wheeze had normal lung function at birth, but lung function growth over the first 6 years was reduced, compared with the other two groups. A follow-up of these children at 11 years of age, has shown that the three groups that wheezed, even though some had lost their symptoms or had been treated, still had reduced lung function compared with those who never wheezed. Thus, it would appear that chronic asthma will impair lung growth in children.

A recent study of more than 1000 children with mild asthma in the USA (2) has shown that asthma duration is associated with reduced lung function (as measured as percent predicted FEV_1). Furthermore, this study found that the decrease in lung function was worse for boys compared with girls.

A recent long-term study showed improvement in lung function to be significantly greater in children who started inhaled corticosteroid treatment early (within 2 years) after the onset of asthma symptoms (3). In addition, these children had better lung function at a lower accumulated dose of inhaled steroid, during the first 4.5 years of treatment, than children who started inhaled steroids after more than 5 years of symptoms. This suggests that early treatment with inhaled steroids may prevent airway remodelling and the development of irreversible structural changes in the airways. In the children who did not receive inhaled corticosteroids (3), the average annual 'loss' of lung function (FEV_1) was approximately 1%, compared with the expected increase over time. These findings strongly suggest that early, rather than late, introduction of inhaled steroid treatment facilitates normal development of lung function.

Verberne *et al.* (4) studied children with mild to moderate asthma treated with either inhaled beclomethasone dipropionate (BDP) or salmeterol for one year. The annual change in lung function (percentage predicted FEV_1) significantly increased in those children receiving BDP, but not in those receiving salmeterol.

Thus, from these and other studies, it can be concluded that children with chronic asthma have reduced growth of lung function compared with non-asthmatic children, and that inhaled corticosteroids improve lung growth so that FEV_1 increases as predicted with age.

Lung Growth

It has been reported that systemic administration of steroids to rats after birth will impair normal alveolar development (5).This appears to be a time-dependent phenomenon since the inhibitory effect of steroids is not apparent when they are administered two weeks after birth. At present, the effect of inhaled steroids on alveolar development in rats has not been studied. Furthermore, the effect of systemic steroids on lung development has not been studied in other species.

In pre-school children, it is often difficult to determine whether they have asthma, or recurrent viral wheeze and therefore there is a risk of giving inhaled

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steroids to children who do not have inflammatory changes in the airways. Based upon the findings in rats, concerns have been raised that administration of inhaled corticosteroids to such patients might interfere with normal alveolar development. At present there are no data to support this and the risk that this would indeed be the case seems very low.

In clinical practice it is extremely rare that inhaled corticosteroids are given to children younger than 6 months of age. If it is appropropriate at all to base risk considerations about inhaled steroids in children upon the findings in rats receiving systemic steroids, then one would not expect exogenous steroids to have any adverse effects at that point in time (Table 1) Further studies are needed both in animals and in children before any conclusions can be made about impairment of alveolar development by inhaled steroids in children.

Long-term growth

Growth during childhood takes place in three phases. During the first two years, there is rapid, but decelerating growth, that is determined mainly by nutrition. Relatively steady childhood growth then follows that is regulated by the growth hormone axis, until the onset of puberty. The third phase, the pubertal growth spurt, is controlled by a combination of growth hormone and sex hormones. Slow prepubertal growth is a characteristic of asthma and appears to be independent of disease severity or treatment (6). Despite a reduction in growth rate, most children with asthma (possibly with the exception of those with very severe disease) attain a normal final height (7). A meta-analysis of the effects of oral and inhaled corticosteroids on growth concluded that final height is not affected by treatment with inhaled corticosteroids(8).

Treatment with low-dose systemic steroids or high-dose inhaled steroids may result in decreased growth velocity, but as long as this is accompanied by a concomittant slowing in development of bone age, the child will eventually reach normal final height. Only if there is a greater effect on growth than on bone age, will there be a problem.

When attempting to determine the effects of inhaled corticosteroids on growth, a large number of different factors have to be taken into account. For example, children with more severe asthma are likely to receive higher doses of inhaled corticosteroids, which will cause greater suppression of growth. However, poorly controlled asthma itself is associated with stunting growth. Also, there may be seasonal factors, such as reduced growth over the Winter period which might appear to increase the suppressive effects of inhaled corticosteroids, since asthma is often less well controlled during Winter. A study of inhaled fluticasone propionate at doses of up to 200 μg/day for up to 52 weeks showed no adverse effect on growth in children (9).

In conclusion, when the dose of inhaled corticosteroid is tailored individually to the severity of the disease and an optimal delivery system is used, inhaled corticosteroids do not adversely affect lung development or long-term growth in paediatric asthma patients.

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